the VO_2-PVA relation (59% increase in INT with EMD vs 44% with DOB; neither drug altered EFF) with normal pH. Acidosis decreased E_{max} by 22%, increased INT by 14%, but did not change EFF [43 ± 12 (SD) vs 38 ± 13]. During acidosis, coronary flow increased (69%) with EMD, but was unchanged with DOB. Compared to DOB, EMD resulted in greater increases in both E_{max} (73% vs 24%) and INT (109% vs 18%) but neither drug altered EFF. In contrast, contractile economy (1/slope of FTI-VO_2 relation) increased (49%) with EMD but decreased (14%) with DOB with both normal pH and acidosis. *Conclusion:* EMD is a more potent inotropic drug than DOB during acidosis. In terms of contractile EFF, EMD does not have an energetic advantage over DOB. However, its effects are more economical.

4:15

809-2 The Na^+-Channel-Modulators BDF 9148 and DPI 201-106 Exert Positive Inotropic Effect Without Direct Interaction With the Contractile Proteins on Human Myocardium

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Only in right ventricular myocardium from patients with dilated cardiomyopathy, but not from nonfailing patients, a Ca^{2+}-sensitizing effect of DPI 201-106 has been described (J Clin Invest (1988) 82: 1578). The present study investigated the effect of the Na^+-channel-modulators BDF 9148 (BDF, 1 μM) and DPI 201-106 (DPI, 1 μM) on the Ca^{2+}-sensitivity of chemically skinned (Triton X, 1%, 20 h, 4ºC) left ventricular muscle fibers (SFB) from patients with dilated cardiomyopathy (DCM, n = 8) and nonfailing patients (NF, n = 7). For comparison, the Ca^{2+}-sensitizer EMD 57033 (EMD, 10 μM) was studied as well.

In electrically stimulated left ventricular papillary muscle strips (1.8 mM Ca^{2+}, 1 Hz) from NF and DCM BDF, DPI and EMD significantly increased force of contraction. In SFB EMD shifted the concentration-response curve significantly to the left in DCM (95% confidential interval of EC_{50} (CI EC_{50}): control: 2.0–2.4 μM; +EMD: 0.5–1.0 μM) and NF (CI EC_{50}: 2.6–3.5; +EMD: 0.4–0.7 μM). *BDF and DPI did not influence the Ca^{2+}-sensitivity* of the contractile proteins towards Ca^{2+} in DCM and in nonfailing myocardium.

It is concluded, that (1) Ca^{2+}-sensitizers increase the sensitivity of the contractile proteins towards Ca^{2+} in DCM and in nonfailing myocardium; (2) BDF 9148 and DPI 201-106 increase force of contraction without increasing the Ca^{2+}-sensitivity of the contractile apparatus in man.

4:30

809-3 Mechanisms of the IGF-1 Positive Ionotropic Action

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Although chronic treatment with insulin-like growth factor-1 (IGF-1) is known to increase cardiac function in humans and rats, its acute cardiac effects and mechanisms of action are largely obscure. IGF-1 was acutely administered in isovolumic buffer-perfused whole heart preparations monitoring functional indexes, and peak intracellular calcium levels, $[Ca^{2+}]_i$, with the aequorin bioluminescence method. Ca^{2+} responsiveness of the myofilaments was assessed by determining the maximal Ca^{2+} activated pressure (MCAP) and the EC_{50} of the peak Ca^{2+}-peak LV pressure relationship. ^{31}P NMR spectroscopy was used to assess intracellular pH, $[pH]_i$, and high energy phosphate metabolism. The maximal positive inotropic effect of IGF-1, observed at a concentration of 10^{-7}, was evident within 60s after the application and persisted after its removal from the perfusate.

Data are mean ± SE; DP = developed pressure; *p < 0.01 vs. baseline.

	DP mmHg	$[Ca^{2+}]_i$ μmol/L	MCAP mmHg	EC_{50} μmol/L	$[pH]_i$ pH units
Baseline	124 ± 4	0.78 ± 0.01	173 ± 8	0.68 ± 0.02	7.15 ± 0.01
IGF-1	150 ± 3*	0.74 ± 0.01*	215 ± 5*	0.66 ± 0.02	7.15 ± 0.01

IGF-1 increased DP by 21% from baseline. This positive inotropic effect was mediated by an increase in myofilaments Ca^{2+} responsiveness, in particular by an increase in MCAP since $[Ca^{2+}]_i$ decreased. $[pH]_i$ and high energy phosphate content did not change during IGF-1 infusion. IGF-1 is a drug with unique properties, acting primarily by sensitizing the myofilaments to Ca^{2+} without modifying high energy phosphate metabolism.

4:45

809-4 LY366634, a Novel Sodium Channel Activator, Improves Left Ventricular Function in Dogs With Chronic Heart Failure

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The hemodynamic effects of LY366634 (LY) {chemical name: (s)-4-[3-[[1-(diphenylmethyl)-3-azetidinyl]oxy]-2-hydroxypropoxy]-1h-indole-2-carbonitrile}, were examined in 7 dogs with chronic heart failure (HF) (LV ejection fraction 26 ± 2%) produced by sequential intracoronary microembolizations. LY was administered intravenously in incremental doses of 3, 5 and 10 μg/kg/min. Each dose was administered for 30 min. Heart rate (HR, min^{-1}), QTc interval (msec), peak LV +dP/dt (mmHg/sec) and LV fractional area of shortening (FAS, %) were measured at baseline and at 30 minutes after the administration of each of the 3 drug doses. FAS was measured from 2-D short axis echocardiograms.

	Baseline	3 μg/kg/min	5 μg/kg/min	10 μg/kg/min
HR	82 ± 6	70 ± 6*	75 ± 7	70 ± 5
QTc	311 ± 9	309 ± 7	325 ± 11	339 ± 17*
+dP/dt	1569 ± 118	1929 ± 137*	2146 ± 116*	2388 ± 155*
LVFAS	27 ± 2	32 ± 2*	37 ± 2*	43 ± 2*

*P < 0.05 vs. Baseline, ANOVA with Students-Newman-Keuls test

LY was not associated with ventricular arrhythmias. It tended to reduce HR and had no effect on QTc interval except at the highest dose used. In addition, LY significantly improved peak LV +dP/dt and FAS. *Conclusion:* In dogs with HF, intravenous LY improves LV systolic function without increasing HR and with little or no prolongation of QTc interval. These findings suggest that LY may be a useful agent for the short-term treatment of patients with advanced HF.

810 Cardiac Arrest and Emergency Care

Wednesday, March 19, 1997, 4:00 p.m.–5:00 p.m.
Anaheim Convention Center, Room C2

4:00

810-1 Post-Resuscitation Left Ventricular Diastolic Dysfunction Successfully Treated with Dobutamine

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Significant left ventricular dysfunction, including both systolic and diastolic, has been documented following successful resuscitation from prolonged cardiac arrest. Successful treatment of post-resuscitation LV systolic dysfunction has been reported with Dobutamine (Dobut). Dobutamine (10 μg/kg/min) was studied for its effect on post-resuscitation diastolic dysfunction in 14 swine. Eight additional swine were also studied as controls. Solid state micromanometer-tipped catheters were used for measurement of left ventricular end-diastolic pressure, and the calculation of the time constant of isovolumic relaxation (Tau). Contrast left ventriculograms were performed to calculate left ventricular volumes. Each animal underwent a 15-minute period of untreated ventricular fibrillation cardiac arrest followed by resuscitation. Data were collected at a pre-arrest baseline and at 5-hours post successful resuscitation. Table 1 shows the improved diastolic function at 5-hours post-resuscitation in the Dobutamine treated animals compared with controls.

	LVEDP (mmHg)	LVEDV (ml)	EDP/EDV (× 100)	Tau (msec)
Baseline				
Controls	11 ± 1	28 ± 6	41 ± 5	28 ± 1
Dobut.	11 ± 1	31 ± 2	38 ± 4	31 ± 1*
5 Hours				
Controls	20 ± 3	28 ± 5	76 ± 11	41 ± 3
Dobut.	9 ± 1*	25 ± 3	47 ± 8*	31 ± 5*

*p ≤ 0.05 vs controls

Dobutamine (10 μg/kg/min) can successfully overcome left ventricular diastolic dysfunction seen 5 hrs. after successful resuscitation from cardiac arrest.